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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,459	04/01/2004	John T. Mulligan	340078.411	8500

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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	**PAPER NUMBER**
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/20/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,459	MULLIGAN ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-15, in the reply filed on November 16, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

2. The information disclosure statement filed July 13, 2004 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has

been placed in the application file, but the information referred to therein has not been considered. Specifically, the IDS filed July 13, 2004 appears to be missing PTO-1449.

Specification

3. The disclosure is objected to because of the following informalities:

(1) The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The hyperlink appears on page 17.

(2) The specification contains a figure on page 16 that should only appear in the drawings. See MPEP 608.01 VI which states, "Graphical illustrations, diagrammatic views, flowcharts, and diagrams in the descriptive portion of the specification do not come within the purview of 37 CFR 1.58(a), which permits tables, chemical and mathematical formulas in the specification in lieu of formal drawings. The examiner should object to such descriptive illustrations in the specification and request drawings in accordance with 37 CFR 1.81 when an application contains graphs, drawings, or flow charts in the specification."

Appropriate correction is required.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-5 and 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al. (Proceedings of the National Academy of Sciences, USA (1997) 94: 6847-6850).

Regarding claim 1, Smith teaches a method of depleting in a sample of double-stranded oligonucleotides a population of double-stranded oligonucleotides containing mismatched bases thereby enriching in said sample a population of double-stranded oligonucleotides containing correctly matched bases, comprising the steps of:

(a) contacting the sample containing double-stranded oligonucleotides with a mismatch recognition protein in solution under conditions to permit the protein to interact with a double-stranded oligonucleotide containing at least one mismatched base (page 6847, column 2 – page 6848, column 1 ("MutHLS reactions" section), where PCR products are contacted with the mismatch recognition proteins MutH, MutL, and MutS)

(b) collecting double-stranded oligonucleotides that have not interacted with said mismatch recognition protein, thereby depleting the population of double-stranded oligonucleotides containing mismatched bases (page 6848, "Forward Mutation Assay" section, where double-stranded PCR products lacking mutations (i.e. products uncleaved by MutHLS treatment) were separated from those products that bound the mismatch recognition proteins by agarose gel electrophoresis and subsequently collected; see also page 6848, see also legend of Table 1).

Regarding claim 2, Smith teaches that prior to the step of collecting, having an additional step comprising separating said double-stranded oligonucleotide containing at least one mismatched base that has interacted with said mismatch recognition protein, from double-stranded oligonucleotides that have not interacted with said mismatch recognition protein (page

6848, "Forward Mutation Assay" section, where the double-stranded PCR products lacking mutations (i.e. products uncleaved by MutHLS treatment) were separated from those PCR products having a mismatched base (i.e. products cleaved by MutHLS treatment) by agarose gel electrophoresis).

Regarding claims 3 and 4, the double-stranded oligonucleotides used by Smith are chemically synthesized by the enzymatic activity of DNA polymerase.

Regarding claim 5, Smith teaches that additional steps comprising denaturing and reannealing occur before treatment of the double-stranded oligonucleotides with the mismatch recognition protein (see page 6847, column 1, "PCR amplification" section, where the double-stranded oligonucleotides are amplified by PCR, a method comprising multiple cycles of denaturation and reannealing, prior to treatment with MutH, MutL, and MutS).

Regarding claim 7, the double-stranded oligonucleotides taught by Smith are double-stranded DNA (see page 6847, column 2, where Smith teaches incubation of PCR products with mismatch repair proteins).

Regarding claim 8, the double-stranded PCR products taught by Smith comprise a portion of a gene (page 6847, column 2, "PCR amplification" section).

Regarding claim 9, Smith teaches that the mismatch recognition protein is MutS (page 6847, column 2, "MutHLS reactions" section).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 10 and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (Proceedings of the National Academy of Sciences, USA (1997) 94: 6847-6850) in view of Burmer et al. (US 5,935,788).

Smith teaches the method of claim 1, as discussed above.

Smith does not teach incorporation of biotin into the double-stranded oligonucleotides or separation via biotin-streptavidin interactions.

Burmer teaches a method of separating multiple populations of nucleic acids, such as homoduplexes and heteroduplexes (see abstract for a general description; column 8, line 55 – column 9, line 14 teach separation of heteroduplex and homoduplex populations).

Regarding claim 10, Burmer teaches contacting a sample containing a mixture of different nucleic acid populations (such as heteroduplex and homoduplex populations) with biotin to generate biotin-labeled nucleic acids (column 8, line 55 – column 9, line 14 teach

separating homoduplexes from heteroduplexes; column 9, lines 15-31 teach biotin incorporation followed by streptavidin capture; see also column 10, lines 35-57 for further discussion of biotin-streptavidin capture).

Regarding claims 13-15, Burmer teaches contacting the biotin-labeled nucleic acids with an avidin, specifically, streptavidin immobilized on a solid support (a column) to separate the populations of nucleic acids (see column 10, lines 35-57).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to separate the error-free PCR products from the error-containing PCR products using biotin-streptavidin capture as taught by Burmer. Burmer taught that, "This direct capture method is preferred as it is likely to be the simplest, least costly and most efficient of the capture technologies available (column 10, lines 55-57)." An ordinary practitioner of the PCR product purification method taught by Smith would have been motivated by these teachings of Burmer to isolate the error-free homoduplex PCR products using biotin-streptavidin capture in order to avoid the more time-consuming gel electrophoresis and purification steps taught by Smith. An ordinary practitioner would have expected a reasonable level of success in using biotin-streptavidin capture in the method taught by Smith, since Burmer taught application of the method to separation of virtually any two nucleic acid populations (column 8, line 55 – column 9, line 14 teach separation of homoduplexes and heteroduplexes; column 2, lines 21-45 teach separation of virtually any two nucleic acid populations). Therefore, an ordinary practitioner of the PCR product purification method taught by Smith, interested in obtaining a more rapid, inexpensive, and simple method of separating error-free PCR products from those products with

errors, would have been motivated to separate the products using biotin labeling followed by streptavidin capture, as suggested by Burmer, thus resulting in the instantly claimed methods.

8. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (Proceedings of the National Academy of Sciences, USA (1997) 94: 6847-6850) in view of Burmer et al. (US 5,935,788) and further in view of Yeung et al. (WO 97/46701; cited on IDS).

The combined teachings of Smith and Burmer result in the method of claim 10, as discussed above.

Neither Smith nor Burmer teach the use of the CEL I mismatch recognition protein.

Yeung teaches methods of detecting mutations using the mismatch recognition protein (CEL I) (see abstract). Yeung teaches that CEL I "recognizes every type of mismatch regardless of the sequence context in which the mismatch resides and the enzyme is active in pH ranges from acidic to basic (see abstract)." Yeung further teaches that CEL I possesses several advantages relative to the MutS protein used by Smith (see Table 5 on page 40), including: recognition of all basepair substitutions, applicability to DNA loops, ability to lower background with DNA polymerase recycling reaction (i.e. PCR), and applicability to long targets.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to substitute CEL I for the MutHLS system in the method taught by Smith. Yeung taught that CEL I was a highly stable mismatch endonculease capable of recognizing all base pair substitutions and also loops (see abstract and Table 5). An ordinary practitioner would have been motivated by these teachings of Yeung to substitute CEL I for the MutHLS system in order to obtain the ability to cleave and subsequently eliminate all mutated PCR products, thereby

improving the purity of the isolated error-free products resulting from the method of Smith. An ordinary practitioner of the method taught by Smith would have been further motivated to substitute CEL I for the MutHLS system, because Yeung taught that, unlike MutS, CEL I was applicable to long targets (1-3 kb – see Table 5; note that the PCR product generated by Smith is 1.6 kb). Finally, an ordinary practitioner would have been motivated to substitute CEL I for the MutHLS system, because Yeung taught that the enzyme lowered background in PCR (see Table 5). Therefore, an ordinary practitioner of the PCR product purification method taught by Smith, interested in improving the ability to cleave PCR products containing mismatched bases, would have been motivated to substitute CEL I for the MutHLS system, as suggested by Yeung, thus resulting in the instantly claimed method.

9. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (Proceedings of the National Academy of Sciences, USA (1997) 94: 6847-6850) in view of Burmer et al. (US 5,935,788) and further in view of Yanagihara et al. (Proceedings of the National Academy of Sciences, USA (2002) 99(17): 11317-11321). The Yanagihara reference was first available online August 12, 2002.

The combined teachings of Smith and Burmer result in the method of claim 10, as discussed above.

Neither Smith nor Burmer teaches that the mismatch recognition protein is MuA transposase.

Yanagihara teaches a method of mapping genetic polymorphisms using MuA (see abstract). Yanagihara teaches that MuA transposase "exhibits a strong target site preference for

all single-nucleotide mismatches (see abstract)." See also Figure 2A and page 11319 where Yanagihara states, "All eight types of mismatched base pairs were efficiently used as target (page 11319)." Yanagihara also teaches that the enzyme shows high sensitivity, as it is capable of cleaving single-nucleotide mismatches in the presence of 300,000-fold excess of non-mismatched sites (see abstract and Figure 3).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to substitute MuA transposase for the MutHLS system in the method of Smith. Yanagihara taught that MuA transposase cleaved all single-nucleotide mismatches with a high degree of sensitivity (see abstract, Figure 2A and Figure 3 cited above). An ordinary practitioner would have been motivated by these teachings of Yanagihara to substitute MuA transposase for the MutHLS system in order to obtain the ability to cleave and subsequently eliminate all mutated PCR products, thereby improving the purity of the isolated error-free products resulting from the method of Smith. An ordinary practitioner would have also been motivated to substitute MuA transposase for the MutHLS system, because Yanagihara taught that the enzyme was highly sensitive and was able to cleave mismatched targets even in the presence of a large excess of non-mismatched target (Figure 3 and abstract). Finally, an ordinary practitioner would have expected a reasonable level of success in using MuA transposase in the method taught by Smith, because Yanagihara used this enzyme with PCR products (see Figures 4 & 5). Therefore, an ordinary practitioner of the PCR product purification method taught by Smith, interested in improving the ability to cleave PCR products containing mismatched bases, would have been motivated to substitute MuA transposase for the MutHLS system, as suggested by Yanagihara, thus resulting in the instantly claimed method.

Conclusion

No claims are currently allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Numerous references teach the method of claim 1, including Lishanski et al. (PNAS (1994) 91: 2674-2678), Wagner et al. (US 6,120,992; cited on IDS), Gifford et al. (WO 93/22457; cited on IDS), Modrich (WO 97/21837; cited on IDS), and Kulinski et al. (Biotechniques (2000) 29: 44, 46, 48; cited on IDS).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Examiner, Art Unit 1637
December 13, 2006

amb

JEFFREY FREDMAN
PRIMARY EXAMINER
(4/5/07